Biomarkers related to diagnosis, prognosis and therapy in thyroid cancer

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ABSTRACT

Thyroid cancer (TC) is among the 10 most common neoplasms worldwide, with increasing number of cases, especially in populations with a high rate of metabolic syndromes and exposure to radiation, proving to be a great challenge to the global health system. Based on this, several studies are carried out in order to identify paths for early diagnosis and more individualized treatments. The main target of the research is biomarkers, which consist of the detection of small molecules, whether genetic material or not, which can be more expressed or suppressed with the presence of the tumor. Among them are cellular-free DNA, microRNAs, oncometabolites, and specific genetic mutations. In this way, biomarkers can contribute to more accurate and earlier tumor specificity and staging, since small quantitative changes can be easily observed. In addition to enabling other types of less aggressive treatments, encouraging permanence during the process. Thus, the present study aims to explore the main biomarkers currently being researched, as well as their roles in the diagnosis, prognosis, and therapy of thyroid cancer.

Keywords: Thyroid Cancer, Tumor Biomarkers, Prognosis, Early Diagnosis.

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine neoplasia, falling into head and neck carcinomas. Currently, it is divided into 5 subtypes, depending on the cell type initially affected. If it derives from follicular epithelial cells, we have papillary, follicular, oncocytic and anaplastic subtypes. If it derives from parafollicular C cells, we will have medullary thyroid cancer. Regarding epidemiological data, papillary thyroid carcinoma is the most common, accounting for 80-90% of cases, but with a good prognosis, unlike anaplastic thyroid carcinoma, which represents 1% of cases, but 20% of annual mortality due to TC (MSD, 2024).

After investigation of the TC subtype with histological instruments to verify the initial cell lineage, the study of the staging of the neoplasm is performed. Currently, the TNM system is used, which focuses on the prognosis of the disease, taking into account the tumor diameter in its largest dimension, its limitation to the thyroid, the level of extrathyroidal extension, lymph node extension, and the presence of metastases (INCA, 2023).

The diagnosis for SC is made through imaging tests, especially ultrasound, which will be the basis for fine needle aspiration puncture (FNA), being the procedure of choice in the evaluation of suspicious nodules. Associated with this, the treatment used today is surgical, with partial or total thyroidectomy being performed, depending on the case, the removal of affected lymph nodes is also performed (INCA, 2023). Therefore, there are several invasive procedures, no matter how routine, affecting the continuity of investigation and treatment due to patients' fear. Based on this, the importance of biomarkers in this process is reinforced, which can be detected by specific blood tests.

Biomarkers can be defined as the result of a body's response to a given situation. They exist naturally within physiology, with specific functions or just being suppressed to maintain control of homeostasis and tumor suppression. However, when a mutation originates a tumor, for example, this event is seen as a given by the body, resulting in the abnormal production of certain molecules and proteins, which can be found in body fluids or tissues. Currently, they are called biomarkers due to their importance in detecting abnormalities, such as thyroid neoplasms (MSD, 2024).

Therefore, it is evident the importance of further studies that explore biomarkers in cases of TC, with the aim of contributing to the increase of specificity in the staging of neoplasia and in more individualized treatments, since different subtypes of TC can result in different levels of biomarkers produced. In this way, initiatives for healing can be done more efficiently and reducing the patient's discomfort during treatment.

DEVELOPMENT

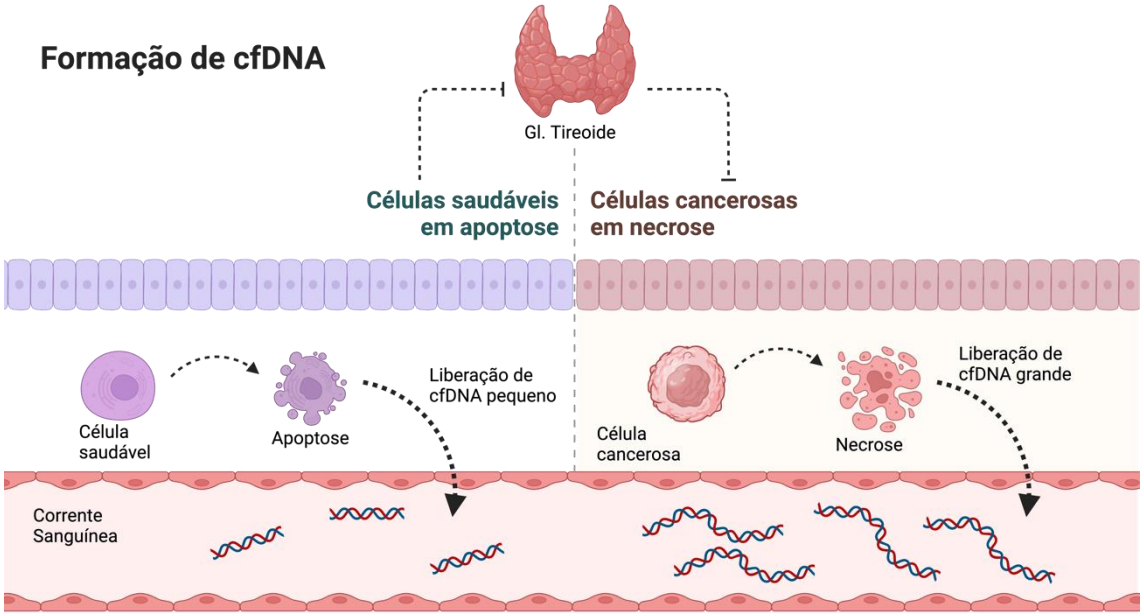
DIAGNOSIS

The diagnosis of TC involves multiple steps, mainly due to the need to stage and classify the disease correctly. The first sign is usually detected in routine exams such as palpation of the thyroid gland and lymph nodes, since this neoplasm is largely asymptomatic (INCA, 2023). Afterwards, more specific exams are performed, such as thyroid function tests, scintigraphy, tomography, ultrasonography and FNA. In the results, some main tumor markers for TC can be analyzed, such as the level of elevated serum thyroglobulin in most cases, and elevated calcitonin levels in cases of medullary thyroid neoplasia (Hou et al., 2023).

However, these analyses are still nonspecific and do not consider several biomarkers currently researched. This is the case of cell-free DNA molecules (cfDNA), which have their concentrations in the blood modified with the presence of tumors and inflammation. Its production is already present in normal physiological processes, but when tumor cells undergo necrosis, they release larger cfDNA, being called circulating tumor DNA (Figure 1). Research by Hou et al. (2023) has shown that combining multiple cfDNA can result in a more accurate diagnosis than with just one cfDNA.

Laboratory analysis of this component can be performed through polymerase chain reactions (PCR) and sequencing techniques, which enable the identification of these genetic materials in peripheral blood samples (Fussey et al., 2018). By using PCR, it was possible to identify the presence of the BRAFV600E mutation in individuals with the neoplasm (Pupilli et al.) and differentiate it from malignant cases (Fussey et al., 2018). In addition, according to Zane et al. (2013), it was possible to identify a higher concentration of cfDNA in patients with papillary SC than in healthy people. Thus, it can be used as an effective biomarker for diagnosis and prognosis.

Figure 1: Illustrates the difference between the size of cfDNAs produced by healthy cells and cancer cells in the context of the thyroid gland.



In addition, microRNAs are other excellent biomarkers that can favor the specificity of the diagnosis of TC. They are endogenous non-coding small molecules whose function is to bind to specific mRNAs, which produces an inhibition response of the protein that would be originated. This process can be beneficial, by suppressing the expression of tumor suppressor proteins, but it can be harmful by preventing the gene expression of tumor suppressors, thus favoring oncogenesis (Geropoulos et al., 2022).

Tumor characteristics also result in different miRNAs, such as tumor size, location, extrathyroidal extension, lymph node metastases, etc. It is also noteworthy that after a thyroidectomy, about 31 circulating miRNAs are altered, two of which are associated with recurrence of papillary TC. Therefore, it is a very present marker that can be detected in blood tests, but there is still a need for more research to specify which tumor miRNAs are, since other cells can also produce them (Geropoulos et al., 2022).

As in the case of free DNA molecules, miRNAs can offer more accurate diagnoses if their serum expressions are combined with the use of ultrasonography, as detected by Zhang et al. (2007). The researchers combined miR-222, miR-221, miR-146b, and miR-21, resulting in a specificity of more than 90% in papillary SC cases. Therefore, biomarkers are increasingly shown to be very efficient in the process of diagnosing TC.

Another group of biomarkers currently being studied are the oncometabolites, which are the metabolites produced by the biochemical processes of cancer cells, which differentiate them from healthy cells. Several molecules are part of this group, such as glucose, fumarate, succinate, asparagine, glutamine, lactate, among others. This is due to the fact that cancer cells need to maintain their metabolism accelerated for growth, with a greater capacity to capture glucose and lactate in the

process of aerobic glycolysis, which is capable of modifying the pH of the tumor site (KHATAMI et al., 2019).

In the case of papillary thyroid cancer, a significant increase in mRNA encoding metabolic enzymes was detected compared to healthy patients, which corroborates its importance as a biomarker. The quantification of these markers may contribute to the diagnosis, while high levels of lactate and choline and low levels of citrate, glutamine and glutamate are found in cases of TC. Citrate and lactate stand out as the most significant oncometapolites (KHATAMI et al., 2019).

Thus, the diagnosis stage is extremely important when elucidating the characteristics of the tumor, such as size and metastases, as well as its specific biomarkers. This set of information serves as a basis for the prognosis and the treatment that will be performed.

PROGNOSIS

The prognosis of CT refers to the possible referrals that the neoplasm may follow based on what is known today. This process mainly takes into account the tumor characteristics present in the staging (diameter, metastases, lymph nodes, etc.) and the history of disease recurrence. Tumor multifocality is also a negative prognostic aspect, as it is associated with central lymph node metastasis, being a risk factor for the extrathyroid region (Cui et al., 2022). Based on this, it is possible to draw a profile of how the tumor will proceed and grow, with the aim of applying the most appropriate therapies.

Tumor characteristics are caused by genetic mutations, which can be hereditary or acquired throughout life. The BRAFV600E mutation is one of the best known in the case of TC, it is more related to recurrence and mortality in cases of papillary thyroid cancer (Cui et al., 2022).

Other mutations can lead to elevated expression of biomarkers, such as CD133 related to poor prognosis in cases of medullary thyroid carcinoma; CD44 is a regulator of tumor epithelial transformation and is related to poor overall survival; CD24 with a positive prognosis related to better survival and no recurrence; CD10 highly expressed in anaplastic thyroid carcinoma; CD15 related to improved survival without recurrence; and ALDH1 linked to the mediation of resistance to chemotherapy drugs and cellular detoxification (Peng et al., 2024).

TREATMENT

The *American Thyroid Association* defines cure for TC as the absence of clinical or radiographic evidence of a tumor, and undetectable serum thyroglobulin levels. To this end, the information present in the diagnosis (subtype of the neoplasm and its staging) and prognosis (recurrence and genetic aspects) are analyzed.

Some specific mutations may contribute to this phase of treatment, such as CD133-expressing cells, which may be better treated with radioactive iodine. On the other hand, cells that express CD44 show greater proliferative capacity and greater resistance to treatment, as is the case with ALDH1, but this is an important prognostic factor exclusive to TC, having high potential in future therapies (Peng et al., 2024).

Treatments are currently based on surgical procedures, which are extremely invasive, as is the case with medullary thyroid cancer, in which the *British Thyroid Foundation's recommendation* is a total thyroidectomy and central nodal clearance with lateral clearance of the neck if there is evidence of central nodal disease (Cosway et al., 2022).

After thyroidectomy, postoperative radiation therapy may be performed with the goal of removing all thyroid tissue. It allows for better screening in cases of recurrence of the neoplasm and helps in the interpretation of thyroglobulin levels during recovery. If the disease is of intermediate or high risk, levothyroxine is applied in order to suppress the thyrotropin concentration and prevent the growth of TC again. Monitoring is done based on periodic thyroglobulin and antithyroglobulin antibody tests and ultrasonography with an interval of 5 years after post-surgical monitoring (MSD, 2023).

The choice of surgery can be avoided depending on the size of the tumor, as long as ultrasound follow-up is maintained. Another option in cases of small tumors is hemithyroidectomy, which can offer a better quality of life to the patient and has a good prognosis (MSD, 2023).

CONCLUSION

TC is a global health problem on the rise, even though it does not present high levels of mortality, it is a silent disease that in most cases is asymptomatic. In addition, after being discovered, the treatments offered today are mostly surgical, which makes them invasive and implies patient adherence. Based on this, research has been carried out on new forms of early and more specific diagnosis, among them, we have biomarkers.

Biomarkers are molecules that are more expressed or suppressed compared to healthy individuals, which can indicate the presence of tumor cells in the thyroid gland, as well as their subtype and staging. Among the main biomarkers are cellular-free DNA, miRNA, and oncometapolites. These provide guiding parameters about tumor extension and the most specific treatment that can be used. As for prognosis, the analysis of genetic markers is extremely important since some mutations are related to greater tumor recurrence, better prognosis or resistance to chemotherapy.

Thus, with the greater number of studies in the area, tests for biomarkers can contribute to the early detection of TC through simple blood tests, which would make them more viable for the

population compared to FNA testing. In addition, treatments could be more individualized and more effective, avoiding surgical procedures and follow-ups for the rest of life.

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